

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/24/2008 has been entered.

Status of Claims

1. All previously pending claims are canceled. Claims 14-18 are added.

Drawings

2. Replacement drawings were received on 03/24/2008. These drawings are not acceptable. Figures 2,3,6 remain to be illegible. Reference to publication of applicants having legible color drawings is not sufficient.

As stated previously, If the only way of presenting the drawings in question in legible way is color drawings, applicant is invited to submit the color drawings.

The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

A. Claim 14: In this new version of the base claims, applicant omits recitation of the step of using LGA_S analysis and addresses it as "generating the local-global alignment score". However, turning to specification, it is clear that "generating the local-global alignment score" means using LGA_S analysis (see p. 22, for example). Therefore, for "generating the local-global alignment score" one needs understanding of calculations using LGA_S analysis. As addressed in the previous rejections, using LGA_S analysis is vague and indefinite as specification, in the section defining the scoring function LGA_S (p. 17), fails to identify variables k , X , $S(F)$, $S(LCS)$, w^* used in calculation of the scoring function; thus, the function is undefined.

Further, as indicated previously, applicant refers to publication of A. Zemla providing the details of the calculations. Such reference is not sufficient. Calculation of the scoring function LGA_S is subject matter essential for conducting method as claimed. Incorporation of essential material in the specification by reference to a foreign

application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 U.S.P.Q. 157 (C.C.P.A. 1973); *In re Hawkins*, 486 F.2d 579, 179 U.S.P.Q. 163 (C.C.P.A. 1973); and *In re Hawkins*, 486 F.2d 577, 179 U.S.P.Q. 167 (C.C.P.A. 1973).

B. Claim 15: It is not clear whether the “further” steps address in the claim are in fact the steps preceding the steps of claim 14 as they produce “correspondence” that is then analyzed by the steps of claim 14. The method of claim 14 addresses generating an alignment score for a particular correspondence, whereas the claims of the dependent claim 15 addresses generating plurality of scores for plurality of correspondences to arrive – not clear how? – at a single correspondence.

C. Claim 16: It is not clear how a new correspondence is being generated based on number of pairs and on longest segment as claimed. Does it involve method steps different from those in claim 14, and if not, what is the difference of “new” correspondence from those addressed in claim 14.

Claim Rejections - 35 USC § 112, first paragraph (New Matter).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is made for the following reasons:

Claim 14: The claim introduces new term "global distance metric". The term "global distance metric" is not defined in the specification. The definition of the term in claim 18

identifying plurality of distance scores, wherein each distance score corresponds to a number of pairs of residues in the correspondence that are within a pre-determined distance of a plurality of pre-set distances

is not supported by the language in the specification which addresses global distance test, GDT as

GDT_v--an estimation of the percent of residues (largest set, not necessary continuous) that can fit under the DISTANCE cutoff of v Angstroms (p. 17, paragraph [0036]).

Consequently, both the term "global distance metric" in claims 14,18, and the manner in which the "distance scores" are defined in claim 18, are considered as a new matter.

Claim Rejections - 35 U.S.C. § 101(utility)

5. Applicant's arguments and Declaration of Dr. Zhou have been considered and were deemed persuasive. The rejection is withdrawn.

Claim Rejections - 35 U.S.C. § 101 (non-statutory invention)

6. Claim 14-18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 14-18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to a process. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

The instant claims do not produce a tangible result. The last step of claim 14 is directed to storing the score. Neither the claim nor specification indicate where the score is stored (memory, Internet, etc....), therefore, as such the method does not include a real world result. For example, method as claimed may take entirely within the confines of a computer without any communication to the outside world. A tangible

requirement requires that the claim must set forth a practical application of the computational steps to produce a real-world result. No practical result is recited in the claims; thus the instant claims do not include any tangible result.

Claim Rejections - 35 USC § 102.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of the previously pending claims over Lackner et al. is withdrawn.; Examiner agrees with applicant's argument that In Lackner, root mean square and distance analysis are applied independently based on a same correspondence.

7. Claims 14-18 are rejected under 35 U.S.C. 102(b) as anticipated by Zemla et al. (Proteins: Structure, Function, and Genetics vol. 45, Issue S5, Pages 13-21. Published Online: 28 Jan 2002) or Cristobal et al. (BMC Bioinformatics 2001, 2:5. Published 1 August 2001).

The instant claims are drawn to method of generating a local-global alignment score which indicates a global and a local similarity between a first protein structure and a second protein structure, the method comprising:

receiving a protein structure correspondence wherein a plurality of positions in the protein structure correspondence indicates a corresponding pair of residues in the first protein structure and the second protein structure;

identifying a longest contiguous segment comprising a plurality of contiguous positions in the correspondence, wherein the root mean square deviation of a set of pairs of residues within the segment is less than a specified threshold value;

identifying a global distance metric based on a number of pairs of residues in the correspondence that are within a pre-determined distance of each other;

generating the local-global alignment score based on the longest contiguous segment and the global distance metric; and

storing the local-global alignment score

Zemla et al. teach global distance test (GDT) software and its extension include the local-global alignment package (LGA).

With respect to identifying a global distance metric based on a number of pairs of residues, in the reference, the global distance test (GDT) summary graphs provide an approximate sorting of predictions by quality and a good starting point for further analysis (Fig. 3). These plots consist of points identifying subsets of structure that can be fitted under a specified distance cutoff. Similarity between predicted and experimental structures may be assessed over regions that are not necessarily continuous in sequence. p. 16, left column. In particular, the GDT_TS (total scores) measure provides a reasonable single-value approximation of the tertiary structure prediction quality. Total scores, GDT_TS provide a single-value approximation of the tertiary structure prediction quality. The GDT_TS is defined as an average of four

separate GDT calculations identifying maximal sets of residues at 1, 2, 4, and 8 Å distance cutoffs. Paragraph bridging pages 16-18.

With respect to identifying a longest contiguous segment comprising a plurality of contiguous positions, in the reference, a comparison of secondary structure assignments in the target and model, and the longest continuous segment (LCS) analysis are carried out. These plots identify precisely the LCS in the model structure that do not deviate from the target by more than a specified $C\alpha$ RMSD. p. 16, left column.

Further, as sequence-dependent superposition methods are unable to identify regions of structural similarity in a prediction that are not correctly aligned by sequence, sequence-independent LGA algorithm is being used.

Similarly, Cristobal et al. teach LGA program for structure comparative analysis of two selected 3D protein structures. The LGA analysis can be made in two general modes (see last section of the article):

- Alignment dependent analysis. This mode can be used when two protein structures are identical by the numbering of their amino-acid sequences. Under this mode (LCS and GDT analysis) the program is able to identify the segments where two structures are identical, and the segments where they differ.
- Alignment independent analysis. This mode can be used for structural comparison of any two proteins. The best superposition (according to the LGA technique) is calculated completely ignoring the alignment relationship between the two proteins. The suitable amino acid correspondence (structural alignment) is reported.

Art Unit: 1631

The LGA algorithm searches for the best structural alignment of two proteins according to the LCS and GDT scores calculated for each analyzed alignment independent superposition.

The measures LCS and GDT established for detection of local and global structural similarities between two proteins were successfully verified during the CASP process providing a very good ranking of the evaluated protein models.

When comparing two protein structures the LCS procedure is able to localize (along the sequence) the Longest Continuous Segments of residues that can fit under the selected RMSD cutoff, while the Global Distance Test (GDT) algorithm is designed to complement evaluations made with LCS searching for the largest (not necessary continuous) set of "equivalent" residues deviating by no more than a specified DISTANCE cutoff. The combined LCS and GDT scores produce the LGA-S number which is used to determine the best structural alignment.

The additional LGA-Q value reported in the output from the LGA program is calculated for the final superposition. This number ranks the quality of the alignment and is obtained from the formula: $Q = 0.1 \cdot N / (0.1 + \text{RMSD})$, where N denotes the number of residues superimposed under the specified distance cutoff (by default 5), and RMSD is the root mean square deviation calculated on these residues. For rather "weak" alignments the LGA-Q is less than 2.0.

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed or fully envisioned by the teaching of the references cited above

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cristobal et al. (BMC Bioinformatics 2001, 2:5. Published 1 August 2001).

Cristobal reference teaches, in part, that for automatic assessment of protein structure the best approach is to combine sequence-independent and sequence-dependent methods. See section "Conclusion". The limited list of sequence-independent and sequence-dependent methods is provided in Table 1. As one of sequence-dependent methods, the reference describes the Global Distance Test which is an estimation of the largest number of residues that can be found where all distances between the protein structures are shorter than the cutoff distance. The number of residues is measured as a percentage of the length of the target structure. The measure used is GDT TS, which is the average of four measures with D = 1,2,4 and 8 Å. see

fifth page of the reference, left column. As a sequence-independent method, the reference such method as LGA which utilizes LCS procedure to localize (along the sequence) the Longest Continuous Segments of residues that can fit under the selected RMSD (see discussion of the reference in the rejection under USC 102(b) above.

In *KSR Int'l v. Teleflex*, the Supreme Court, in rejecting the rigid application of the teaching, suggestion, and motivation test by the Federal Circuit, indicated that

The principles underlying [earlier] cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.

KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007).

Applying the KSR standard of obviousness to the reference of Cristobal, Examiner concludes that the combination of sequence-independent and sequence-dependent methods is an "obvious to try" choosing from a finite number of identified, predictable solutions. Cristobal suggests that it will benefit automated assessment of protein structure to combine sequence-independent and sequence-dependent methods. The claimed combination is thus were obvious because it would have been obvious to try the known methods for comparing 3D protein structures, with a reasonable expectation of success.

Conclusion.

9. No claims are allowed

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./

Primary Examiner, Art Unit 1631